PROPOLIS – A MEDICINE

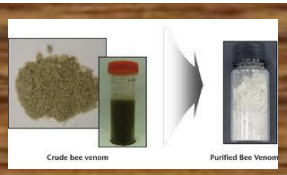
Dr. Biochem. Cristina Mateescu
Institute for Apicultural Research and Development
Bucharest, Romania
APIMONDIA Scientific Commission of Apitherapy
Louvain-La Neuve – Belgium 2013

Bee products – food or medicines?

- Bee products are now subject to an increasing interest from both consumers and producers. And if producers are concerned than the spectrum of possibilities meant to be used comprise both **medicines** – in this case **propolis** – **food or nutritional supplements (functional food)** and cosmetics. That is why an attentive review on the legal status of the bee products on the international market seems to be an important issue in valuing the beekeeping production.



Product	Nutritional value	Therapeutic importance
Bee pollen	**FOOD**	**Medicine**
Honey	**FOOD**	*Medicine*
Royal jelly	*Food*	**Medicine**
PROPOLIS	None	**MEDICINE**
Bee venom	None	**Medicine**

Role of the European Medicines Agency
Propolis as medicine

- It is a fundamental requirement that decisions about the authorization of medicines are ***based on an objective, scientific assessment of their quality, safety and efficacy***.
- The primary role of the EMEA is to conduct these assessments. Through its **scientific committees**, the EMEA ***assesses every medicine for which a marketing-authorization application has been submitted*** (in accordance with the centralized procedure), and prepares a recommendation (called an 'opinion') that is then relayed to the European Commission, which has the ultimate responsibility for taking decisions on granting, refusing, revoking or suspending marketing authorizations.

PHARMACEUTICAL DOSSIER

- Every pharmaceutical product dossier should contain the following data:
- **expert advice** (formulation, technology, technical specifications etc.),
- **technological process**,
- technical specification,
- **validation procedures,**
- **scientific references** and of course,
- **CLINICAL STUDIES**.

Propolis - definition

It is the resinuous, sticky material collected by honeybees from various parts of the plants (trees, bushes,etc.) buds, exudates and is known to have been used as a folk medicine since around 300 BC.

Propolis or “bee glue” is a resinous, solid, dark colored material (brown, yellow-brown or green), with a compact waxy consistency.

- Theories on the origin of propolis

NATURAL SOURCES OF PROPOLIS

- The main propolis components can be identified in the vegetal sources visited by bees. Quite often, the bees visit plant from the family of the coniferous, poplars (*Populus sp*.) as well as other species: *Fagus sylvatica, Aesculus hippocastanum*. In Europe, the main sources of propolis comprise species of *Alnus spp., Betula spp (birch tree)., Corylus spp. (hazel tree), Quercus spp (oak tree)., Populus sp., Salix spp. (willow tree)*
- In the USA the main species are the *poplar* and the *pine*. According to the works of KONIG (1985), the poplar buds represent the main sources of propolis in Europe, South America, West Asia and North Africa.
- For other geo-botanical regions the situation is the following:
- *Acacia Karroo* a tree in South Africa
- *Xanthorrhoea pressii* and *Xanthorrhoea australis* in Australia and regions with tropical climate

NATURAL SOURCES OF PROPOLIS

- The buds and the bark of some bushes as *Plumeria accuminata, Plumeria acutifolia, Schinus terebinthifolius* and *Psidium guajava* in the Pacific islands, especially in Hawaii
- Recent studies on the botanical origin of propolis collected from the south american continent, especially in Brasil, proved the existence of some specific compounds found in several plants like: *Araucaria angustifolia, Eucalyptus globulus* and *Rosmarinus officinalis* and *Bacharis sp.*

Propolis – legal status

Natural medicines - Herbal preparations

- The term **'herbal preparation'** is equivalent to the European Pharmacopoeia's definition of a 'herbal drug preparation', i.e. "... preparations obtained by subjecting [herbal substances] to treatments such as ***extraction, distillation, expression, fractionation, purification, concentration*** or fermentation." (Ph. Eur. 2005).
- In order to get medicines or supplements, bee propolis is subject to such treatments.

PHYSICO-CHEMICAL PROPERTIES OF PROPOLIS

- Its smell is complex; sometimes balsam-like, reminding of wax, honey and vanilline. When burnt, the smoke has a typical aroma of balms and resins of the finest quality.
- Propolis is insoluble in water and only partially soluble in alcohol, acetone, ether, chloroform, propylenglycol, benzen, dimethylsulfoxide, ethylendiamine.
- Depending on temperature, not only the dissolution speed varies, but also the solubility or insolubility of certain fractions are different e.g. wax, which is dissolved in hot alcohol, but is hardly soluble in cold alcohol.
- The residues left after dissolving propolis are generally represented by impurities and foreign bodies, sometimes together with some fractions which might remain partially or totally insoluble, depending on the selectivity of the solvent.

Biological activity of propolis extracts

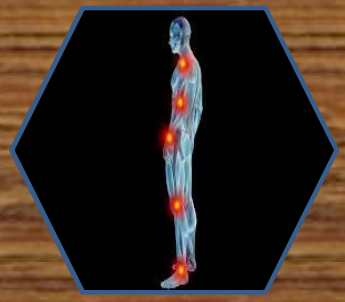
- **The most important compounds in propolis are natural flavonoids that might be modified by an enzyme existing in the honeybee saliva.**

The most important properties atributed to flavonoids are:

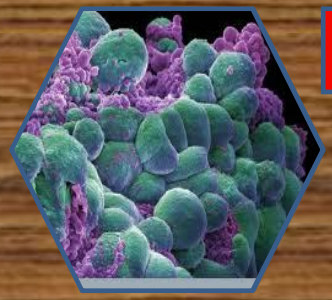
- **Antimicrobial properties (Ghisalberti, 1979)**
- **Antiinflammatory (ASPIRIN-LIKE)**
- **Antioxidant**
- **Increase and protect vitamin C (ascorbic acid) in relation with the action on capillary vessels (Ravina, 1969)**
- **i.e. decrease the permeability of capillaries (vitamin P action (Szent Gyorgyi, 1936)**
- **Stabilize collagen through inhibiting the hyaluronidase**
- **Anti-haemorrhage**
- **Influence *in vitro* of some flavonoids on the enzymatic metabolism of mucopolysaccharides from saphenous veins (Niebes and Luszt, 1971).**

Biological activity of propolis extracts

Antimicrobial, antifungal, antiviral

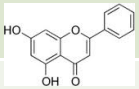
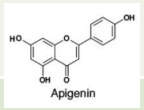
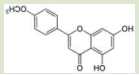
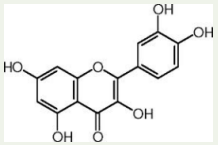
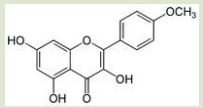


Anti-inflammatory, analgesic, anasthetic

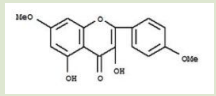
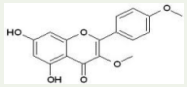
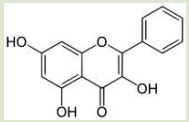
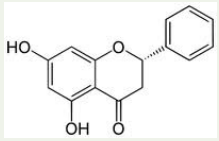


antitumoral

Main propolis compounds and their actions

Compound	Action
Chrysine 	gives the colour of beeswax (Jaubert, 1926) **tumour toxicity** (Hladon et al., 1987)
Apigenin 	**healing agent of gastric ulcers**
Acacetin 	anti-inflammatory action (Bankova et al., 1987)
Quercetin 	hystaminopexic activity (Di Maggio and Ciaceri, 1961); **anti-viral (Konig and Dustmann, 1985)** strenghening capillaries (Budavari, 1989) **anti-tumoral activity (Matsuno, Tetsuya, 1991)** spasmolytic
Kaempferide 	spasmolytic anti – *Micobacterium phlei* anti-acid resistant microorganisms

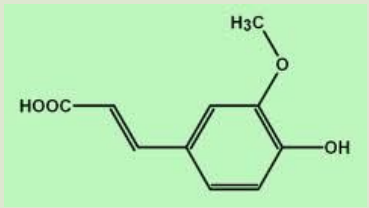
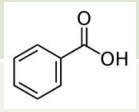
Main propolis compounds and their actions

Compound	Action
Kaempferol-7,4'-dimethyl ether 	anti-mycotic
Ermanin 	anti-mycotic
Galangin 	bacteriostatic activity (Villanueva et al., 1964) anti-microbial and anti-mycotic (Metzner et al., 1979) **anti- *Heliocobacter pylori* (MIC 25 ug/ml)**
Pinocembrin (mountain propolis) 	bacteriostatic activity anti-mould (Miyakado et al., 1976) anti- *Blastomycetes* (Metzner et al., 1977) anti-microbial and anti-mycotic, in vitro and external use (Metzner et al., 1979) anti- *Candida* (Metzner et al., 1978) local anaesthetic (Paintz and Metzner, 1979) **anti- *Heliocobacter pylori*** (MIC: 12.5 ug/ml)

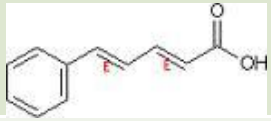
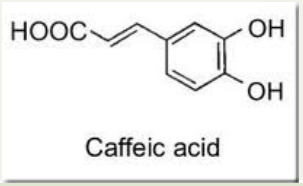
Main propolis compounds and their actions

Compound	Action
Pinobanksin	anti-microbial and anti-mycotic (Metzner et al., 1979)
Pinobanksin-3-acetate	anti-microbial and anti-mycotic
Pinostrobin	local anaesthetic
3',4'–dihydroxyflavonoids	strengthening capillaries (Roger, 1988)
Flavan-3-ols	strengthening capillaries (Roger, 1988)
Pectolinaringenin	spasmolytic
Luteolin	**antiviral (Konig and Dustmann, 1985)** **healing of gastric ulcers**
Artepillin C	**anti-tumour effect; anti-leukemic effect** anti- *Microsporus, Arthroderma*
Eriodictyol	helping pulmonary insufficiency prevention of acute pulmonary insufficiency
Pinosylvin (3,5-dihydroxystilbene)	anti-microbial against *B. subtilis* and *B. cereus.* Anti-mycotic against *Mycobacterium phlei* and *M.Smegmatis.*

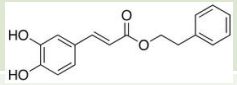
Main propolis compounds and their actions

Compound	Action
Ferulic acid** 	antibacterial effect (gram-positive and gram-negative microorganisms); agglutinant effect (useful in treating slowly healing wounds by help of a soft propolis extract); collagenic effect (described in 1938); promote build-up collagen and elastin (two esential components in the matrix of connective tissue)**;
Isoferulic acid	anti *Staphylococcus aureus*
Benzoic acid 	bacteriostatic and bactericide effects balsamic and antiseptic
Cinnamic acid	anti- *Staphylococcus aureus*
Cinammic acid derivatives	increase the wound healing and the regeneration of epithelium
Isopentyl ferulate	anti-influenza virus A/Hong Kong (113N2) *in vitro* inhibits the production of hemagglutinins *in ovo*

Main propolis compounds and their actions

Compound	Action
Cinnamylidene acetic acid 	antimicrobial against *Bacillus subtilis, Bacillus cereus, Escherichia coli.* antimycotic against *Mycobacterium phlei, M.smegmatis, Candida albicans.*
Aromatic acids and their esters	antifungal and antibacterial properties
p-Coumaric acid benzyl ester	antimicrobial and antimycotic
Caffeic acid  Caffeic acid	antiviral antibacterial activity on some gram-positive and gram-negative microorganisms anti-inflammatory
Prenyl caffeate* **	**Potential contact allergen (beekeepers)**
3-methyl-but-2-enyl-caffeate	antiviral
Caffeic acid esters	local anaesthetic

Main propolis compounds and their actions

Compound	Action
Caffeic acid phenethyl ester CAPE 	**anti-tumour activity**
Methyl caffeate	**Tumour toxicity or inhibition**
Methyl ferulate	**Tumour toxicity or inhibition**
Diterpenoids of clerodane	**anti-tumour activity** anti-bacterial
2,2-dimethyl-8-prenyl-chromene-6-propenoic acid	**anticancer (anti-tumour) activity**
17-hydroxycleroda-3,(13Z)-dien-15-oic acid	**anticancer (anti-tumour) activity**
Pterostilbene	anti-diabetic (non-confirmed)
VOLATILE COMPOUNDS (etheric oils)	anti-microbial activity

Main propolis compounds and their actions

Compound	Action
Bisabolol	antiinflammatory
Volatile substances in beehive air	anti-hay fever
Arginine (Arg)	stimulates mitosis and enhance protein biosynthesis (Gabrys, 1986)
Proline (Pro)**	promotes build-up collagen and elastin (two essential components in the matrix of the connective tissue) (Gabrys, 1986)**

Propolis - other compounds

- **As reported, propolis contains also:**

  Vitamins **:** ***vitamin B1, B2, B6, nicotinic acid, pantothenic acid, vitamin A, vitamin C and vitamin E.***

- ***Minerals*** **: the most abundant** ***are: copper*** **– 26.5 mg/kg, and** ***manganese*** **– 40 mg/kg. The ash of propolis contains*:*** ***iron, calcium, aluminium, vanadium, strontium, magnesium and silicon.***

- ***Enzymes****: succinic dehydrogenase, glucose-6-phosphatase, adenosine triphosphatase, acid phosphatase* **(TIKHONOV, MOMONTOVA, 1987). These compounds as well as the** ***aminoacids*** **reported are due to the presence of pollen in the composition of propolis.**

BIOLOGICAL ACTIVITIES OF PROPOLIS DEPENDING ON ITS ORIGIN





Origin of propolis	Anti-bacterial	Anti-inflammatory	Anti-tumoral	Hepato-protective	Antioxidant	Allergenic
EUROPE (Poplar)	Flavonones, flavones, phenolic acids, phenolic acids esters	Flavonones, flavones, phenolic acids, phenolic acids esters	**Caffeic acid phenethyl ester (CAPE)** quercetine,	Caffeic acid, ferulic acid, Caffeic acid phenethyl ester (**CAPE**	Flavonoids, phenolic acids, phenolic acid esters	3,3-dimethyl caffeate
BRAZIL (*Baccharis)*	Prenylated p-coumaric acids, labdanic diterpenes	Non-identified	**Prenylated p-coumaric acids, clerodane diterpenoids benzofurans**	Prenylated p-coumaric acids, lignans, flavonoids, caffeoyl-quinic acids	Prenylated p-coumaric acids, flavonoids	Non – examined yet
CUBA	Prenylated benzophenones	Non examined	**Prenylated benzophenones**	Non examined	Prenylated benzophenones	Non examined
TAIWAN	Non examined	Examined flavonones	**Prenylated flavonones**	Examined flavonones	Prenylated flavonones	Examined flavonones

Propolis antibiotic (antibacterial)

- When applied topically propolis is active against several bacteria and other microorganisms;
- It is active against several bacterial strains which became resistant to chemical antibiotics.
- The concentration of flavonoids in propolis can directly destroy bacteria, fungi and methycillin-resistant *Staphylococcus aureus;*
- Propolis increases the action of chemical antibiotics.
- At thus propolis can be used in various infectious diseases: respiratory, Othorhinolaryngological, gastric (*Helicobacter pylori)*, skin and dental infections

Propolis antiviral action

Herpes virus **: 2 types**

Type 2 (HSV-2) causes genital herpes

Type 1 (HSV-1) causes cold sores and sometime genital herpes

Famvir, Valtrex, Zovirax, are among the medications used to treat the symptoms of herpes.

Test tube studies show that **propolis can stop HSV-2 and HSV-1 from reproducing.**

Applying a 3% propolis cream might improve healing of recurrent HSV-2 lesions.

Study: 90 men and women with recurrent HSV-2 divided in 2 groups

Treatment: propolis ointment and acyclovir ointment and placebo; after 10 days, 80% of the propolis group were healed versus 47% in the acyclovir group and 40% in the placebo group. The topical propolis cream produced better results than Zovirax cream, a medication usually prescribed to treat genital herpes outbreaks.

Propolis antiviral action

Warts: produced by **HPV (human papilloma virus infection)**.

The virus causes keratin, a hard protein in the epidermis to grow too fast.

As reported in the *INTERNATIONAL JOURNAL OF DERMATOLOGY* in November 2009, scientists identified that propolis shows strong activity against warts. In a 3-months –study, 135 patients with different types of warts received oral propolis, echinacea or placebo.

In patients with common warts treated with propolis, cure was achieved in 75% and 73% of patients respectively.

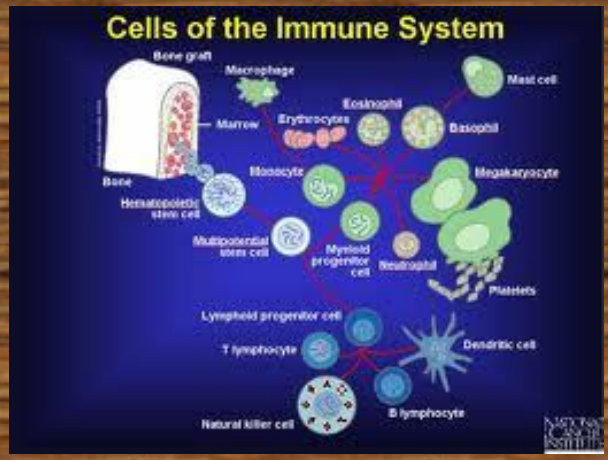
The conclusion was that propolis is a safe and effective immunomodulating therapy for common warts.

Propolis immunomodulatory

- Propolis has been used empirically for centuries and it was always mentioned as ***an immunomodulatory agent***. In recent years, *in vitro* and *in vivo* assays provided new information concerning its mechanisms of action.
- *In vitro* and *in vivo* assays demonstrated the ***modulatory action of propolis*** on murine peritoneal macrophages, increasing their microbicidal activity. Its stimulant action on the **lytic activity of natural killer cells against tumor cells**, and **on antibody production** was demonstrated.
- Propolis ***inhibitory effects on lymphoproliferation*** may be associated to its anti-inflammatory property.
- In immunological assays, the best results were observed when **propolis was administered *over a short-term* to animals.**

Propolis –immune system

- There **are 2 effects of propolis**: **inhibition of cellular growth**; it can increase the presence of certain white immune cells like *T-lymphocytes,* increasing hydrogen peroxide production without any simultaneous and damaging nitrite production which usually occurs with *macrophage* activity.
- In an article published in 2007 in the *JOURNAL OF ETHNOPHARMACOLOGY, it was* reported **that propolis increases the activity of macrophages and natural killer cells** and the **production of antibodies.**
- Another way in which propolis aids the immune system is its ability to **strengthen phagocyte feature.** Phagocytes are the white blood cells that protect the body by ingesting harmful foreign particles, bacteria and dead or dying cells.

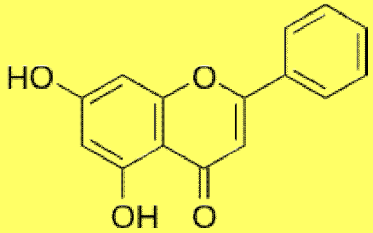


Propolis anti-allergic action

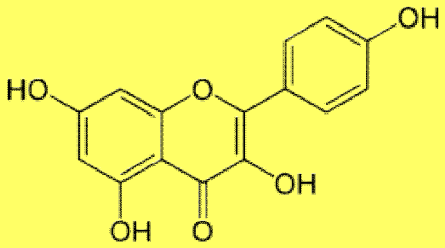
- Propolis is considered to **down-regulate type I allergy**, but the effective components of propolis remain unknown. In addition, propolis components vary depending on the area from which they are collected due to variations among wild plants in an area.
- In a study the effects of **water and ethanol extracts of propolis** from Brazil and China on **mast cell degranulation** and cytokine production were compared.
- All propolis extracts ***inhibited degranulation*** from antigen-stimulated RBL-2H3 cells, but the effective doses differed according to collection areas. **The ethanol extract of Chinese propolis**, which ***was the strongest inhibitor of mast cell degranulation***, was divided into compounds using normal- and reversed-phase liquid chromatography.

Propolis anti-allergic action

- **The isolated anti-allergic components were identified** as **chrysin**, **kaempferol** and its derivative, and chrysin was revealed to inhibit IL-4 and MCP-1 production from antigen-stimulated RBL-2H3 cells. HPLC quantification also revealed the Brazilian propolis extract to contain only small amounts of these flavonoids, which suggested that variation in propolis components could affect anti-allergic properties.
- ***Chrysin***

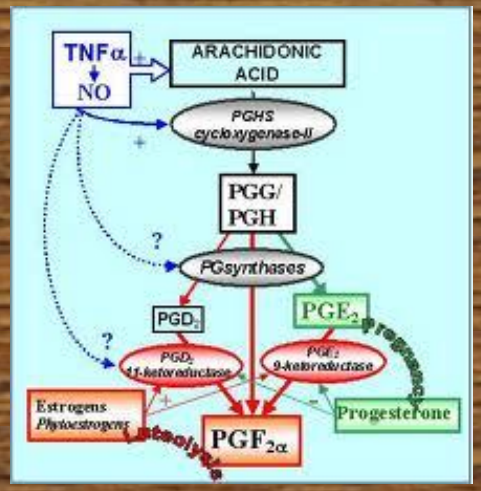


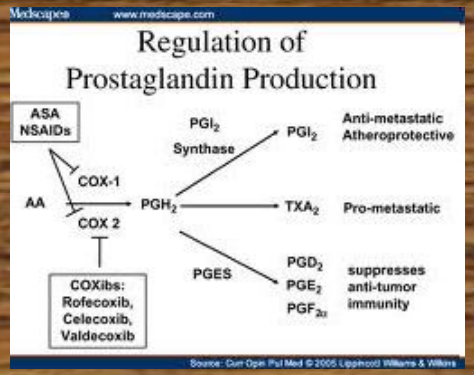
Kaempferol



Analgesic action

- Some painful processes appear as a result of prostaglandins occurrence at the place of the lesion (wound).
- The synthesis of these **prostaglandins can be stopped by flavonoids due to their inhibiting action on the enzyme PG-cyclooxygenase.**

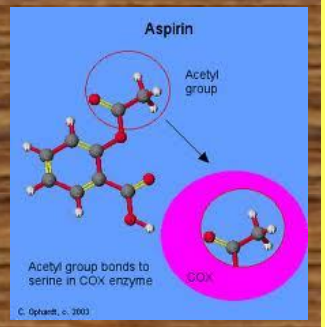




Inhibition of prostaglandin synthesis

- The effect of an **ethanolic extract of propolis**, with and without **CAPE**, and some of its components on cyclooxygenase (COX-1 and COX-2) activity in macrophages has been investigated.
- COX-1 and COX-2 activity, measured as prostaglandin E_2 (PGE_2) production, were concentration-dependently inhibited by propolis.
- Among the compounds tested ***pinocembrin*** and ***caffeic, ferulic, cinnamic and chlorogenic acids*** did not affect the activity of COX isoforms.
- Conversely, **CAPE** and ***galangin*** were effective, the last being about ten-twenty times less potent.

Aspirin-like, anti-inflammatory action



- Flavonoids and phenolics inhibit – the same way as Aspirin - acetylsalycilic acid does – the enzyme responsible for the synthesis of prostaglandins – **PG-cyclo-oxygenase .**This is the main reason why flavonoids are known as **natural aspirin.**
- **CAPE (**caffeic acid phenethyl ester) an active compound in propolis has been proven to show anti-inflammatory activity, suppressing leukotriene production by the peritoneal macrophages.
- **Propolis** presented also an ***inhibition of the plaquetary aggregation (aspirin-like)***and of the eicosanoid synthesis.

Anti-tumour (anti-cancer) action

Tumour cell	Reported outcome	Dose and route	*In vivo / in vitro*	Main groups or active compounds	Authors/ characterization
HL-60 (human leukemia)	Apoptosis-like DNA fragmentation	1-200 μg/ml	*In vitro*	**Artepillin C** (3,5 diprenyl-4-hydroxycinammic acid)	Matsuno et al., (1997) (HPLC)
HLC (lung cancer), HGC (gastric cancer), hepatoma, melanoma	Suppression of tumour growth; ↑ ratio of CD4/CD8 T cells	500 μg (i.t.)	*In vivo*	**Artepillin C**	Kimoto et al., (1998) NM
Yac1 –cells (murine lymphoma)	↑ Natural killer activity	10% (p.o)	*In vivo*	**Prenylated – p-coumaric acid**; benzopyranes, essential oils, aromatic acids, di- and- triterpenes	Sforcin et al., (2002) GC, GC-MS, TLC

Anti-tumour (anti-cancer) action

Tumour cell	Reported outcome	Dose and route	*In vivo / in vitro*	Main groups or active compounds	Authors/ characterization
Colon carcinogenesis	↓ Aberrant crypt focci	10,30,90 mg/kg (p.o)	*In vivo*	**Prenylated – p-coumaric acid**; benzopyranes, essential oils, aromatic acids, di- and- triterpenes	Bazo et al., (2002) GC, GC-MS, TLC
C6 glioma cells;	↓viability; ↑apoptosis	10-400μM	*In vitro*	**CAPE**	Lee et al., (2003) NM
MCa (transplantable mammary carcinoma)	↓ tumor nodules ↑apoptosis and necrosis	WSD (50 and 150 mg/kg; caffeic acid and CAPE (50 mg/kg); quercetin (1200 mg/kg) p.o.	*In vivo*	Not Mentioned	Orsolic et al., (2004); NM

Anti-tumour (anti-cancer) action

Tumour cell	Reported outcome	Dose and route	*In vivo / in vitro*	Main groups or active compounds	Authors/ characterization
Canine transmissible venereal tumor	↑ Cytotoxicity	10-200 µg/100ml	*In vitro*	**Prenylated – p-coumaric acid**; benzopyranes, essential oils, aromatic acids, di- and- triterpenes	Bassani-Silva et al., in press
Human pancreatic cancer cells such as PANC-1	non-apoptotic pathway + necrotic-type morphologic changes. cytotoxicity (PC_{100})	10 µg/mL 12.5 µM.	*In vitro*	(6a*R*,11a*R*)-3,8-dihydroxy-9-methoxyptero carpan (**21**, DMPC) **Brazilian red propolis**	Suresh Awale et al., 2008
Urinary bladder tumor cells	Cytotoxity without affecting the normal epithelial cells		*In vitro*	**Ethanolic extract of propolis**	Orsolic et al., 2009

Anti-tumour (anti-cancer) action

- The antitumoral action of propolis is mainly due some of its compounds: **caffeic acid derivatives, flavonoids, artepillin, 2,2-dimethyl-8-prenyl-chromene-6-propenoic acid, 17-hydroxycleroda-3,(13Z)-dien-15-oic acid, etc.**

Clerodane diterpenoid was reported to have potent ***cytotoxic activity*** against:

- **human hepatocellular carcinoma HuH13,**
- **lung carcinoma HLC-2,**
- **HeLa (human cervical carcinoma cells),**
- **KB** and **rat W3Y cells.**

According to Dr. Matsuno, **clerodane diterpenoid** shows ***selective toxicity*** against tumour cells and **stops the cell development cycle** in the gene synthesis phase (phase S).

Anti-tumour (anti-cancer) action

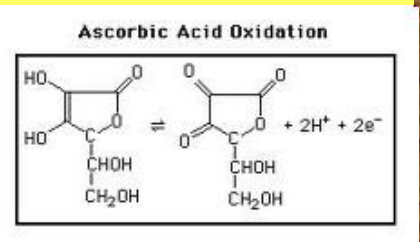
- **Artepillin C,** according to the studies of Dr Kimoto, has also a **strong cytotoxic effect** on various cultured tumour cells and transplanted carcinoma cells.
- 18 types of cultured tumour cells were tested and **artepillin C** showed a ***noticeable inhibitory effect*** on their growth, at doses ranging between 10 and 100 μg/ml.
- A new substance – water soluble – **[artepillin C]-Na** proved to be even more efficient in its anticancer effects. This substance inhibits the **DNA synthesis of cancer cells and malignant lymphoma.**
- The anti-tumour activity of these compounds is also supported and synergetically helped by the anticancer activity of the **phenolic compounds**.

Propolis – anticancer mechanisms

- **Breast cancer (BC) patients** use alternative and natural remedies more than patients with other malignancies. Specifically, 63-83% use at least one type of alternative medicine and 25-63% use herbals and vitamins.
- Propolis is a naturopathic honeybee product, and **CAPE** (caffeic acid phenethyl ester), is ***a major medicinal component of propolis***.
- **CAPE**, in a concentration dependent fashion, inhibits MCF-7 (hormone receptor positive, HR+) and MDA-231 (a model of triple negative BC (TNBC) tumor growth, both *in vitro* and *in vivo* without much effect on normal ***mammary cells*** and strongly influences gene and protein expression.
- It induces **cell cycle arrest, apoptosis and reduces expression of growth and transcription factors, including NF-κB.**
- Notably**, CAPE down-regulates** mdr-1 gene, considered responsible for the resistance of cancer cells to chemotherapeutic agents.

Antioxidant action of propolis

- **PROPOLIS** is **a natural mixture of antioxidants with synergetic activity**
- **Propolis antioxidative activity is shown in several studies *in vitro* and *in vivo*.**
- **This antioxidative activity results in many of the clinical effects obtained when propolis preparations are used.**
- **One of the most impressive effects of propolis is that connected with its protective activity against irradiation (especially gamma, but also that noted with UV-rays). The production of free radicals in organisms exposed to these radiations has as result the tissue damage.**
- **Water propolis extracts used, showed an inhibiting effect on the associated increase of lipid peroxidation as well as an enhancement of SOD activity in the exposed organisms.**
- **The *in vitro* studies showed also that the same WPE shows,by the same antioxidant activity a *good hepatic protection*. It protects against the release of glutathion-dependent lactate dehydrogenase and against the formation of lipid peroxides.**
- **Speaking also about synergetic effects of propolis compounds, we must mentione the antioxidative effects of the propolis balsams, shown through the inhibition of methyl linoleate autooxidation, by active benzyl caffeate.**

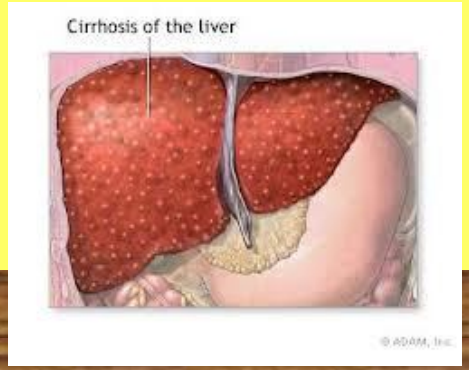


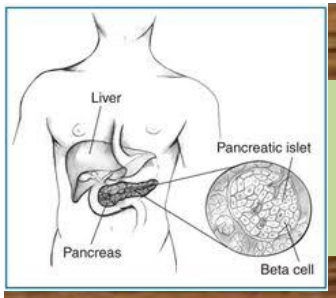
Radioprotective action

- Another important action of propolis is the **radioprotective action.**
- **Radio-opaque** solutions of propolis may be applied topically (**propolis ointment with lanoline**) to prevent the occurrence of **radiodermitis** due to X-ray therapy or radiotherapy in cancer treatment.
- The propolis containing pharmaceutical products can accelerate healing of the lesions produced by these types of therapy.


Anti-xenobiotic activity (anti-toxic) of flavonoids /propolis

- **Flavonoids and in this case propolis proved to be an excellent natural product – show a strong inhibiting effect against the xenobiotics (toxic compounds) as in case of induced CCl-4 intoxication of liver as well as alcohol intoxication. Carbon tetrachloride produces a very toxic and reactive free radical involved in lipids peroxidation or covalent link with essential macromolecules in the hepatocytes.**
- **Bioflavonoids participate as antioxidants in the metabolism of these xenobiotics through the enzymatic *system of oxidases with mixed function*; it is a well known fact that the enzymatic activity is the first target of toxic substances and their derivatives. The protective effect is specially seen at the levels of important enzymes (*succinic dehydrogenase (SDH), glutamate dehydrogenase (GDH) and citocrom oxidase*.**





Effects of propolis in diabetes

Propolis and its direct and indirect hypoglycemic effect

- Laboratory studies on animals treated with propolis showed an increase of the number of Langerhans islets and as a result a hypersecretion of insuline.
- Increased insuline level determines a decrease of blood glucose level and an enhanced accumulation of glycogen in the liver and other organs. A conclusion can be drawn: **propolis extract potentiates the hypoglycemiant action of insulin.**
- **Ethanolic Extract of Propolis (EEP**) offers a promising therapeutic value in prevention of diabetes and dyslipidemic profile.
- **Studies have also shown that PWE (propolis water extract) showed a very strong free radical scavenging activity (Matsushige et al.,1995) as well as IL-1β and NO synthase inhibiting activities.**
- **If not accepted as a MEDICINE, propolis** could be at least an effective **functional food** to prevent the development of insulin resistance induced by fructose-drinking rats in animal models that received 15% fructose solution in drinking water for 8 weeks.

Effects of propolis in diabetes

Conclusions (article published in 2012)

- Propolis preparations are able to attenuate diabetic hepatorenal damage, probably through its anti-oxidative action and its detoxification process as well as the potential to minimize the deleterious effects of free radicals on tissue.
- The protective role of propolis against the ROS induced damages in diabetic mice gives a hope that they may have similar protective action in humans.

Wound healing mechanism

- **The *pharmacodynamics* of propolis wound healing capacity** consists in 2 main steps:
- **blocking of the infectious agents activity** and **starting of the mucolytic and cleaning effects on the necrotic area;**
- **stimulation of the granulation process** – thus favouring the natural reaction of the organism to activate the regenerative processes and an **intensification of epithelial proliferation.**

These processes are accompanied by **an improvement of the blood and lymphatic circulation** of the propolis treated areas, a **diminution of the permeability of the blood vessels(the so-called vitamin P action due to flavonoids - Vitamin P (permeability factor)** is a term applied formerly to a group of plant flavones (**hesperedin, eriodictin, quercetin, rutoside).**

Wound healing mechanism

In **chronic ulcers of the limbs** propolis contributes to **restructuring of the capillary membranes, the occurrence of the neoformation vessels and the improvement of the local cell and tissue metabolic processes through:**

- reduction of the tissue anoxia
- restarting of the enzymatic activities
- favouring the restructuring of the disorganized fundamental substance.
- limiting the spreading of the cicatrices and reducing some side phenomena: budding, eczema formation.

General and local anaesthetic action

- Propolis is one of the products which proved to be a **very good anaesthetic** agent.
- In **local applications** it shows a 3,5 fold higher anaesthetic activity than **cocaine** and 5,2 folds higher than **procaine.**
- In doses consisting of 0.012 g / kg b.w. it produces, on animals a ***general anaesthesia lasting 45 minutes***.
- Applied orally, in veterinary surgery (sheep and dogs) the anaesthetic effect is installed within 2-5 minutes and the animals shows no modification of the pulse, respiration and temperature and no abolition of the reflex excitability.

Propolis in neuro-psychological disorders

- Propolis proved to be an excellent mean in the treatment **neuro-psychical disorders, etc.**
- In the **neuro-psychiatric disorders: stress syndrome, astenia, migraine, and restoring the sleep-awaken equilibrium,**
- **multiple sclerosis,**
- **progressive muscular distrophy, Parkinson disease,**
- **subjective syndrome of cranial traumatisms,**
- **mental anorexia etc.**

propolis proved also to be beneficial.

- **Water propolis extracts (WPE)** are reported to have a **STRONG EFFECT** on the **autonomic nervous system with peripheral action on nervous transmission, and vasodilatation of the blood vessels.**

Propolis dosing

Adults (18 years and older)

- A wide range of doses has been studied for various conditions.
- **A 5% ointment/cream/aqueous solution of propolis** applied in the form of vaginal dressings/douche daily has been used for 7-10 days for acute cervicitis or vaginitis.
- To treat recurring **canker sores**, a dose **of 500 milligrams of propolis has been taken orally daily.**
- A dose of **10 milliliters of 0.2% to 10% propolis ethanol extract mouthwash** (swished in the mouth for 60-90 seconds, then spit out) has been used once or twice daily for **dental plaque.**
- For **genital herpes simplex virus infection**, a **3% propolis skin cream (made from 75-85% concentrated propolis extract**) has been applied to the skin four times daily for 10 days. In cases of cervical or vaginal lesions, the same amount of ointment has been applied to the tip of a tampon and inserted vaginally four times daily for 10 days. Safety and effectiveness have not been established.

Propolis dosing

- A dose of two **250 milligram propolis capsules** has been taken by mouth three times daily for three days to treat bacteria in the urine.
- A **20-30% propolis extract** has been taken by mouth for **five days** to treat giardiasis (milligram dosing not clearly described). Safety and effectiveness have not been established.
- A dose of **2 milliliters of aqueous propolis extract** has been injected every 14 days for up to seven months for Legg-Calve-Perthes disease/a vascular necrosis of the hip. Effectiveness and safety have not been established, and dosing should only be under the supervision of a qualified healthcare professional.

Propolis dosing

- A **10% ethanol extract of propolis** has been taken by mouth over five days for **giardiasis** (milligram dosing not established). Note that ethanol (alcohol) preparations should be used cautiously.
- In children In Romania, the effectiveness have been established and the treatment has been successfully applied especially in children previously submitted to Flagyl or Fasigyn (metronidazole) treatment.
- A **0.5 milliliter propolis nasal spray** (Nivcrisol®) has been used once weekly for five months in preschool children (average age six years) and school-age children (mean age nine years) over a five-month period to treat respiratory infections
- An herbal preparation (Chizukit) containing 50 milligrams per milliliter (mg/mL) of echinacea, 50 mg/mL of propolis, and 10 mg/mL of vitamin C, or placebo (5 milliliters and 7.5 milliliters twice daily for ages 1-3 years and 4-5 years, respectively) has been used for 12 weeks. However currently it is considered that there is not enough scientific evidence to support the use of propolis for respiratory tract infections.

Adverse reactions

Allergies

- It is recommended that **patients avoid propolis** if they experienced allergic/hypersensitivity reactions to propolis, *Populus nigra* L. (black poplar), poplar bud, bee stings/bee products (including honey), or Balsam of Peru. There are multiple reports of swelling, fluid collection, redness, burning, eczema, swelling, fever, and other allergic reactions (including a severe allergic reaction called anaphylaxis) with repeated use of propolis on the skin. Propolis has been linked to several cases of contact dermatitis in beekeepers. Allergic contact stomatitis has been associated with the therapeutic use of propolis.
- eczema contact dermatitis stomatitis



Propolis: Side Effects and Warnings

- **The safety of propolis has not been thoroughly studied**. Although there are some case reports of allergic reactions to propolis, it is generally well tolerated in most adults.
- **Allergic reactions** may cause swelling, redness, eczema, or fever. Propolis may irritate the skin and may cause burning, peeling lips, irritation, lesions, itching, swelling, psoriasis, or eczema. Case reports of irritation in and around the mouth have occurred after use of propolis lozenges or extract taken by mouth.
- **TOXICITY DATA FOR PROPOLIS ARE LIMITED**. Early studies have found propolis to be **RELATIVELY NON-TOXIC**. There has been one report of kidney failure with the ingestion of propolis that improved upon discontinuing therapy and worsened with re-exposure.

Propolis: Interactions with Drugs

- Many tinctures contain high levels of alcohol and may cause nausea or vomiting when taken with metronidazole (Flagyl®) or disulfiram (Antabuse®). This is however not the case of water extracts or soft propolis extracts which contain no alcohol.
- **Propolis may produce additive effects when taken with antimicrobial drugs.**
- Propolis ***may interact*** with the following: anticoagulants, *H. pylori* agents, antibiotics, anti-cancer agents (antineoplastics), antifungals, anti-inflammatories, infertility agents, anti-HIV agents (antiretrovirals), immunosuppressants, and osteoporosis agents.

Propolis interactions with Herbs and Dietary Supplements

- Balsam of Peru and propolis are both known to cause **allergic sensitization** in some people and have multiple compounds in common, such as benzyl benzoate, benzyl cinnamate, benzyl alcohol, benzoic acid, cinnamic acid, caffeic acid, cinnamic alcohol, and vanillin.
- **An increased risk of allergic sensitization may occur if both products are used together.**
- Propolis may interact with the following herbs and supplements: anticoagulants (such as coumarin and licorice), antibacterials, anti-cancer agents (antineoplastics), antifungals, anti-inflammatories, antioxidants, fertility agents, anti-HIV agents, immunostimulants, immunosuppressants, and osteoporosis agents.

PRODUCTS


プロポリス
スプレー
PROPOLIS SPRAY
MIPRO SEPT
10 supozitoare
PROPODERM crema
PROPODERM crema
FarmaVerde
PROPOLIS EXTRACT
Proposept
Tinctura de propolis
Supliment alimentar
MEL-propo

CONCLUSIONS

- With a correct assesment and based on **clinical studies, propolis** may become **a precious natural medicine** used as such or as a complementary tool in classical western medicine;
- A **standardization** of propolis is necessary but this seems to be rather difficult if we speak about pharmacological compounds as they vary much depending on the vegetal origin.
- Probably, in the future, propolis as a raw material should be **standardized according to the main biological activities** (antimicrobial, general antioxidant, antitumoral etc.)
- Clinical studies are still necessary and more and more clinical laboratories are now open to this natural product.

PROPOLIS
A HOPE
FOR THE FUTURE!
THANK YOU FOR
YOUR ATTENTION!
MERCI BEAUCOUP!